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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,481	RABBANI ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-626* is/are pending in the application.

4a) Of the above claim(s) *1-250,288-624 and 626* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *251-287 and 625* is/are rejected.

7)☒ Claim(s) *251-287* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed April 11, 2007 is acknowledged. Claims 1-626 are currently pending. In the response, claims 286, 287, and 625 were amended. Claims 1-250, 288-624, and 626 are withdrawn from consideration as being drawn to a non-elected invention.

This application has been reassigned to Examiner Angela Bertagna in Art Unit 1637 whose correspondence information appears that the conclusion of this Office Action. This Office Action includes new grounds of rejection not necessitated by Applicant's amendment (see sections below), and therefore, is made non-final.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/896,897, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112

for one or more claims of this application. The earlier-filed '897 application does not provide adequate support for claims 251-287 and 625 of the instant application, because it does not teach primer extension using primers containing 3' terminal nucleotides that comprise nucleotide analogues with substitutions on the 2' position of the ribose ring. Accordingly, claims 251-287 and 625 have not been accorded benefit of the earlier-filed '897 application, and the instant application filing date (October 24, 2003) has been used for prior art purposes.

Specification

3. The disclosure is objected to because of the following informalities: The specification recites nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID number on pages 34, 38, and 42. Also, Figures 4 and 5 recite nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID number either in the figure or in the "Brief Description of the Drawings'" section.

Appropriate correction is required.

Claim Objections

4. Claims 251-287 are objected to because of the following informalities: These claims recite "a non-inherent UDT." The acronym UDT should be written out prior to its use as an acronym in order to clarify the claim language. Appropriate correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 251-264, 269-273, 275, 281-286, and 625 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1 201 768 A2; newly cited).

Lin teaches methods for generating cDNA libraries from cells (see Figure 1 and column 2, line 42 – column 3, line 16).

Regarding claims 251, 264, and 281, Lin teaches a method for synthesizing one or more copies of a library of target nucleic acids comprising:

(a) providing:

(i) a library of target RNA molecules (col. 6, lines 10-17 and col. 2, lines 45-51; see also Figure 1, step a)

(ii) primers comprising sequences complementary to homopolymeric sequences in the library of nucleic acid targets (see Figure 1, column 2, lines 52-56, column 6, lines 17-21 and lines 60-65)

(iii) synthesizing reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24).

(iv) addition reagents for addition of a non-inherent universal detection target (UDT) comprising terminal deoxynuclsotidyl transferase (TdT) (column 2, lines 58-65 and column 6, lines 25-32)

(b) annealing the primers to the homopolymeric sequences in the library of target nucleic acids (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21)

(c) extending the annealed primers using the synthesizing reagents to generate at least one copy of the target nucleic acids (see Fig. 1, col. 2, lines 52-56, and col. 6, lines 17-21)

(d) adding a non-inherent UDT to the extended primers (see Figure 1, column 2, lines 58-65, and column 6, lines 25-32).

Regarding claims 252 and 253, Lin teaches that the library of targets is isolated from a biological source (column 6, lines 15-17) or comprises complete or partial copies of nucleic acids isolated from a biological source (see Figure 1, step e and column 6, lines 35-55, where complementary copies of the nucleic acids isolated from the biological source are used as the library of targets from which a complementary copy is synthesized).

Regarding claims 254-258, Lin teaches that the homopolymeric sequences, specifically poly A sequences, are present prior to the isolation of the library of targets from the biological source (see Figure 1, step a and column 6, lines 15-25). Lin further teaches adding another homopolymeric sequence using TdT after the isolation of the targets from the biological sample and preparation of copies using the method of claim 251 (see Figure 1, step c and column 6, lines 25-32).

Regarding claim 261, Lin teaches that the synthesizing reagents comprise Taq polymerase (column 7, line 5).

Regarding claims 262 and 263, Lin teaches that the method of claim 251 further comprises providing:

(a) additional synthesizing reagents for synthesizing a complementary copy of the copy obtained in step (c) (see Figure 1, step c and column 6, lines 43-49)

(b) separating the nucleic acid target from the first nucleic acid copy (see Figure 1, step c and column 6, lines 43-49, where synthesis of the complementary copy by Pwo polymerase inherently results in separation of the target from the first copy)

(c) synthesizing the complementary copy using reverse primers complementary to sequences in the UDT (Figure 1, step c and column 6, lines 43-49, where the poly(dC) primer is taught).

Regarding claims 269-272, the forward and reverse primers taught by Lin comprise a production center since they contain T7, T3, or SP6 promoter sequences which function to produce multiple copies of the target nucleic acid sequence (see Figure 1 and column 6, lines 15-65; see also column 3, lines 28-31).

Regarding claim 273, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55)

(b) providing dNTPs and NTPs (column 6, lines 35-55)

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 275, Lin teaches that the transcription reaction is conducted in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Regarding claims 282 and 283, Lin teaches that the primer is attached to a solid matrix such as a glass slide (see column 5, lines 9-11, where the method is conducted using tissues in slides). In this embodiment of the method, the primer is indirectly attached to the solid matrix via hybridization with the immobilized target.

Regarding claims 284 and 285, Lin teaches that the homopolymeric segment is comprised of poly A, poly T, poly U, poly C or poly G (see Figure 1, column 3, lines 32-39, and column 6, lines 15-65).

Regarding claim 625, Lin teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (col. 6, lines 10-17 and col. 2, lines 45-51; see also Figure 1, step a)

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct

comprises one or more terminal nucleotides at the 3' end (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21)

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24)

(b) annealing the primer or nucleic acid construct to the target nucleic acid (see Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21)

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21).

Lin does not teach that the primers contain 3' terminal nucleotides that are substituted with nucleotide analogues containing a modification at the 2' position of the ribose ring as required by claims 251, 259, and 286. Lin also does not teach the use of chimeric primers as required by claim 260.

Laird teaches PCR amplification using modified primers (see abstract and paragraphs 12-18).

Regarding claims 251, 259, 286, and 625, Laird teaches conducting PCR using primers wherein 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-18). Laird teaches that the modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (paragraph 37).

Regarding claim 260, Laird teaches that the primers contain additional nucleotide analogues (paragraph 20).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Lin. An ordinary practitioner would have been motivated to modify the primers taught by Lin to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). Combining the teachings of Lin and Laird would result in placement of at least one of the nucleotide analogs in the homopolymeric sequence comprising the 3' oligo(dT) tail of the primer taught by Lin. An ordinary practitioner would have had a reasonable expectation of success applying the teachings of Laird to the method taught by Lin since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the method of claims 251-264, 269-273, 275, 281-286, and 625 is prima facie obvious in view of the combined teachings of Lin and Laird.

7. Claims 265-268 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; newly cited) and further in view of Willis et al. (US 6,858,412; newly cited) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052; newly cited).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Neither Lin nor Laird teach including a terminator nucleotide in the TdT tailing reaction as required by claims 265-268.

Regarding claim 266, Lin teaches that the non-inherent UDT is added to a nucleic acid copy by providing TdT and non-terminator nucleotides (Figure 1, step c and column 6, lines 35-55).

Regarding claim 267, Lin teaches that the method of claim 266 further comprises:

(a) providing additional synthesizing reagents for the synthesis of a complementary copy of the nucleic acid copy (column 6, lines 35-55, where Pwo polymerase synthesizes a complementary copy of the UDT-containing copy)

(b) separating the target nucleic acid from the first nucleic acid copy (see Figure 1, step c and column 6, lines 35-55, where upon synthesis of the complementary copy, the target is inherently separated from the first copy)

(c) synthesizing the complementary copy (Figure 1, step c and column 6, lines 35-55).

Willis teaches amplification-based methods of nucleic acid analysis (see abstract and column 4, line 50 – column 5, line 15). Regarding claims 265, 266, and 268, Willis teaches the use of terminal transferase to add chain-terminating nucleotides, such as ddNTPs or acyclic nucleotides, to prevent extension or amplification (see column 26, lines 40-45).

Moran teaches that polymerase-mediated DNA and RNA synthesis reactions often produce molecules with non-homogenous or ragged 3' termini due to spurious template-independent addition of nucleotides by the polymerase (page 2044). Moran teaches that this "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." Regarding claims 265-267, Moran teaches that,

"addition of a single non-coding nucleotide analogue to the 5' terminus of the template DNA strand can result in much more efficient and specific termination at the desired site (3'-end of the product). The use of such 'terminator' nucleotides results in the production of cleaner RNA and DNA oligonucleotide products, often in greater yields, and with more efficient use of nucleotides (page 2044, column 2 – page 2045, column 1)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Willis and Moran to the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to include a terminator nucleotide, such as the dideoxy or acyclic nucleotides taught by Willis, in the terminal transferase tailing reaction taught by Lin, since Willis taught that these nucleotides prevented polymerase-mediated extension, and also since Moran taught that terminator nucleotides reduced template-independent addition of 3' terminal nucleotides by DNA and RNA polymerases (see column 46, lines 40-45 of Willis and pages 2044-2045 of Moran). An ordinary practitioner would have been particularly motivated to minimize template-independent addition of nucleotides by the polymerase, since Moran taught that such addition "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." An ordinary practitioner would have had a reasonable expectation of success in including dideoxy or acyclic nucleotides in the terminal transferase reaction taught by Lin since Willis taught that terminal transferase could incorporate these nucleotides into nucleic acids (column 26, lines 40-45). Thus, the methods of claims 265-268 are prima facie obvious in view of the combined teachings of Lin, Laird, Moran, and Willis.

8. Claims 274 and 276 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; newly cited) and further in view of Sousa et al. (US 5,849,546; newly cited).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Regarding claim 274, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55)

(b) providing dNTPs and NTPs (column 6, lines 35-55)

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 276, Lin teaches that the transcription reaction is conducted in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Lin does not teach inclusion of a mutated RNA polymerase for generation of a chimeric RNA/DNA transcript as required by claim 274.

Sousa teaches methods for synthesizing chimeric nucleic acid molecules using a mutant RNA polymerase (see abstract and column 4, line 53 – column 5, line 31).

Regarding claim 274, Sousa teaches providing reagents for RNA transcription comprising a mutated RNA polymerase, NTPs, & dNTPs and creating a chimeric DNA/RNA transcript (column 9, lines 41-46). Sousa further teaches that RNase A only cleaves RNA after a C or a U, and therefore, replacement of these rNMPs with dNMPs or other nucleotides resistant to nuclease cleavage would prevent this cleavage by RNase A (column 8, lines 55-67).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sousa to the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to utilize the mutant RNA polymerase taught by Sousa to generate chimeric DNA/RNA transcripts since Sousa taught that such transcripts displayed improved resistance to ribonucleases (column 8, lines 55-67). An ordinary practitioner would have recognized that RNase degradation of the transcription product produced in step d of the method outlined in Figure 1 of Lin would be detrimental since the method of Lin required a post-transcription PCR amplification step, and therefore, would have been motivated to minimize the possibility of such degradation by generating a chimeric DNA/RNA transcript as suggested by Sousa. Thus, the methods of claims 274 and 276 are prima facie obvious in view of the combined teachings of Lin, Laird, and Sousa.

9. Claims 277, 278, and 280 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; newly cited) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; newly cited).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Regarding claim 277, although Lin teaches labeling nucleic acid amplification products at multiple stages of the method (transcription and TdT tailing – see column 5, lines 19-23), Lin does not teach including labeled nucleotides in the final RT-PCR amplification step used to generate a copy of the RNA transcription product as required by claim 277.

Regarding claims 278 and 280, Lin teaches labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Regarding claim 277, Steffens teaches including the labeled nucleotide in PCR reactions for incorporation into the resulting products (page 397, column 2). Regarding claims 278 and 280, Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin and Laird, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is prima facie obvious. An ordinary practitioner would also have been motivated to label nucleic acid products generated at any point in the method resulting from the combined teachings of Lin and Laird (e.g. the final RT-PCR step) in order to monitor the yield at each step of the process. An ordinary practitioner would have been motivated to do since Lin taught labeling nucleic acid products produced at multiple steps of the method (see column 5, lines 19-23). As noted above, an ordinary practitioner would have been motivated to utilize the fluorescently labeled nucleotide taught by Steffens to conduct this labeling step, since Steffens taught that the nucleotide permitted

sensitive detection of labeled nucleic acids with minimal background. An ordinary practitioner would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens since Steffens expressly taught its use in PCR amplification (page 397, column 2). Thus, the methods of claims 277, 278, and 280 are prima facie obvious in view of the combined teachings of Lin, Laird, and Steffens.

10. Claim 279 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; newly cited) and further in view of Sousa et al. (US 5,849,546; newly cited) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; newly cited).

The combined teachings of Lin, Laird, and Sousa result in the method of claims 274 and 276, as discussed above.

Regarding claim 279, Lin teaches labeling transcription products using labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Steffens teaches including the labeled nucleotide in PCR and sequencing reactions for incorporation into the resulting products (pages 394-395). Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin, Laird, and Sousa. An ordinary practitioner would

have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin, Laird, and Sousa, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is prima facie obvious. An ordinary practitioner would have had a reasonable expectation of success in using the nucleotide taught by Steffens since Sousa taught that the mutant RNA polymerase was capable of incorporating several different types of modified nucleotides (see column 9, lines 21-40). Thus, the method of claim 279 is prima facie obvious in view of the combined teachings of Lin, Laird, Sousa and Steffens.

11. Claim 287 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; newly cited) and further in view of Borson et al. (PCR Methods and Applications (1992) 2: 144-148; newly cited).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Neither Lin nor Laird teach that at least one of the bases of the nucleotide analogs is different than the base comprising the homopolymeric segment as required by claim 287.

Borson teaches a method for synthesizing cDNA molecules from mRNA templates using a primer comprising an oligo(dT) portion and two additional 3' terminal nucleotides that are different from those in the homopolymeric tail of the primer and template molecules (see page 144, column 3). Borson teaches that inclusion of these two 3' terminal nucleotides "locks the

primer at the beginning of the polyadenylation signal rather than at random points along a potentially lengthy poly(A) tail (page 144, column 3)." Borson further teaches that this "lock-docking" capability of the primer results in improved homogeneity of the resulting products (pages 144 and 146).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Borson to the method resulting from the combined teachings of Lin and Laird. An ordinary practitioner would have been motivated to further include additional 3' terminal nucleotides that were different from the homopolymeric sequence in the oligo(dT) primers taught by Lin since Borson taught that these additional 3' terminal nucleotides locked the primer at the beginning of the poly(A) tail, thereby improving the homogeneity of the resulting cDNA population (see pages 144-146, cited above). An ordinary practitioner would also have been motivated to substitute these 3' terminal nucleotides with nucleotide analogues containing modifications at the 2' position of the ribose ring since Laird taught that these modifications reduced nonspecific amplification (paragraph 37). An ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Borson to the method resulting from the combined teachings of Lin and Laird, since Borson taught that a degenerate set of "lock docking" primers could be used together to amplify cDNA from a diverse mRNA population (page 148). Thus the method of claim 287 is prima facie obvious in view of the combined teachings of Lin, Laird, and Borson.

12. Claim 625 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borson et al. (PCR Methods and Applications (1992) 2: 144-148; newly cited) in view of Laird et al. (EP 1201788; newly cited).

Borson teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (p. 144, col. 3, "mNRA isolation" section)

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (p. 144, col. 3, "Primer Design for cDNA synthesis" section, where the lock-docking primer contains a poly(T) region that is complementary to a poly A sequence in the target and two 3' terminal nucleotides)

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (p. 145, col. 1, "cDNA synthesis" section)

(b) annealing the primer or nucleic acid construct to the target nucleic acid (p. 145, col. 1, "cDNA synthesis" section)

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (p. 145, col. 1, "cDNA synthesis" section).

Borson does not teach that the 3' terminal nucleotide(s) of the primer contain 2' substitutions to the ribose ring.

Laird teaches PCR amplification using modified primers (see abstract and paragraphs 12-18). Regarding claim 625, Laird teaches conducting PCR using primers wherein 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-13). Laird teaches that the modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (see abstract and paragraph 37).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Borson. An ordinary practitioner would have been motivated to modify the primer taught by Borson to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). An ordinary practitioner would have had a reasonable expectation of success applying the teachings of Laird to the method taught by Borson since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the method of claim 625 is prima facie obvious in view of the combined teachings of Borson and Laird.

Response to Arguments

13. Applicant's arguments, see page 120, filed April 11, 2007, with respect to the objections to claims 286 and 287, have been fully considered and are persuasive. Applicant's amendment overcomes the objections, and therefore, they have been withdrawn.

Applicant's arguments, see pages 121-123, filed April 11, 2007, with respect to the rejection of claims 251-287 under 35 U.S.C. 112, 2nd paragraph, have been fully considered and are persuasive. The rejections are withdrawn.

Applicant's arguments, see page 124, filed April 11, 2007, with respect to the rejection of claim 625 under 35 U.S.C. 102(e) as being anticipated by Laird have been fully considered and are persuasive. Laird does not teach all of the elements of amended claim 625, and therefore, this rejection has been withdrawn.

Regarding the rejection of claims 251-264 and 269-287 under 35 U.S.C. 103(a), Applicant's arguments filed April 11, 2007 have been fully considered but they are not persuasive. Applicant argues that since Lin does not state that nonspecific amplification is problematic in the disclosed method, there is no motivation to apply the teachings of Laird to the method taught by Lin (see pages 125-126). This argument was not found persuasive, because as discussed above, an ordinary practitioner would have been motivated to reduce the possibility of nonspecific amplification when practicing the method of Lin by utilizing the 3' terminal modifications to the 2' position of the ribose ring taught by Laird. Although Lin did not teach that nonspecific amplification was a problem in the disclosed method, an ordinary practitioner would have nevertheless been motivated to take steps to ensure that nonspecific amplification did not occur when practicing the method of Lin, and therefore, would have been motivated to

utilize the modified primers taught by Laird. The Federal Circuit has recently provided a detailed explanation of the requirement for motivation to combine in Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651 (Fed. Cir. 2006), noting,

> "Indeed we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example, because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunites by improving a product or process is universal - and even common-sensical – we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references."

The Dystar court clarifies that motivation exists when the improvement made results in a more desirable product or process, and the issue devolves to whether the ordinary artisan possesses the knowledge rendering him capable of combining the references. Here, the ordinary practitioner is a PhD with years of experience. As noted in Dystar, "If, however, as we have held as a matter of law, the level of skill is that of a dyeing process designer, then one can assume comfortably that such an artisan will draw ideas from chemistry and systems engineering – without being told to do so (Dystar at page 1653)." In the instant case, an ordinary artisan reading the Lin and Laird references, would have recognized without being told to do so, that use of the modified primers taught by Laird in the method of Lin would result in a more desirable process by reducing nonspecific amplification. An ordinary practitioner (a PhD with years of experience) also would have possessed the knowledge rendering him capable of obtaining and utilizing the modified primers of Laird in the method of Lin. Thus, an ordinary practitioner would have been motivated to apply the teachings of Laird to the method of Lin with a

reasonable expectation of success. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Regarding the rejection of claims 265-268 under 35 U.S.C. 103(a), Applicant's arguments filed April 11, 2007 have been considered, but are moot in view of the new grounds of rejection.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Angela Bertagna
Art Unit 1637 AMB
July 31, 2007

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JEFFREY FREDMAN
PRIMARY EXAMINER
7/31/07